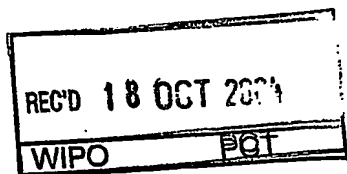




INVESTOR IN PEOPLE



The Patent Office  
Concept House  
Cardiff Road  
Newport  
South Wales  
NP10 8QQ

EP04/10960

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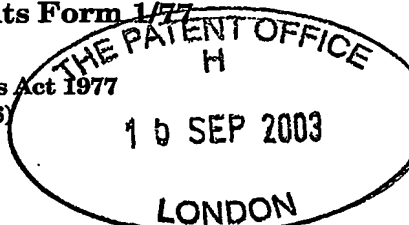
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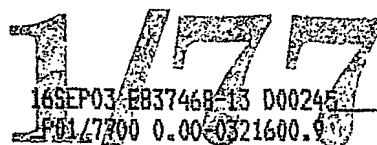
*R. Mahoney*

Dated

18 June 2004



The  
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Office**



# **Request for grant of a patent**

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**15 SEP 2003**

**The Patent Office**

Cardiff Road  
Newport  
Gwent NP10 8QQ

1.	Your reference	4-33361P1/HO 88		
2.	Patent application number (The Patent Office will fill in this part)	0321600.9		
3.	Full name, address and postcode of the or of each applicant (underline all surnames)	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND		
	Patent ADP number (if you know it)			
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND 07125487005.		
4.	Title of invention	Organic Compounds		
5.	Name of your agent (If you have one)	Craig McLean		
	"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB		
	Patents ADP number (if you know it)	07181522002 ✓		
6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. (see note (d))	Yes		

## Patents Form 1/77

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Continuation sheets of this form

Description 34 /

Claim(s) 3 /

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination and search (*Patents Form 9/77*) 1 /

Request for substantive examination (*Patents Form 10/77*)

Any other documents  
(please specify)

11.

I/We request the grant of a patent on the basis of this application

Signature

Date



Craig McLean

15 September 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Mr. T. Drew

01403 32 3069

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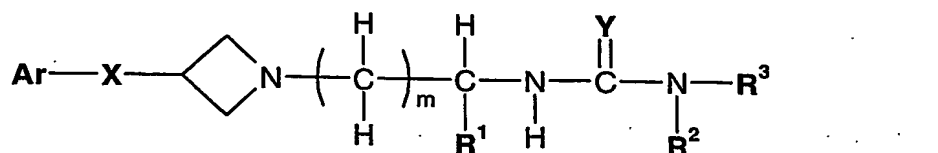
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## ORGANIC COMPOUNDS

This invention relates to organic compounds, their preparation and their use as pharmaceuticals.

In one aspect the invention provides compounds of formula I



in free or salt form, where

Ar is phenyl optionally substituted by one or more substituents selected from halogen, C<sub>1</sub>-C<sub>8</sub>-alkyl, cyano or nitro;

X is -S-, -S(=O)- or -S(=O)<sub>2</sub>-;

m is 1, 2, 3 or 4;

R<sup>1</sup> is hydrogen or C<sub>1</sub>-C<sub>8</sub>-alkyl optionally substituted by hydroxy, C<sub>1</sub>-C<sub>8</sub>-alkoxy, acyloxy, halogen, carboxy, C<sub>1</sub>-C<sub>8</sub>-alkoxycarbonyl, -N(R<sup>4</sup>)R<sup>5</sup>, -CON(R<sup>6</sup>)R<sup>7</sup> or by a monovalent cyclic organic group having 3 to 15 atoms in the ring system;

Y is oxygen or sulfur;

R<sup>2</sup> is hydrogen, C<sub>1</sub>-C<sub>8</sub>-alkyl or C<sub>3</sub>-C<sub>10</sub>-cycloalkyl and R<sup>3</sup> is C<sub>1</sub>-C<sub>8</sub>-alkyl substituted by phenyl, phenoxy, acyloxy or naphthyl, or R<sup>3</sup> is C<sub>3</sub>-C<sub>10</sub>-cycloalkyl optionally having a benzo group fused thereto, a heterocyclic group having 5 to 11 ring atoms of which 1 to 4 are hetero atoms, phenyl or naphthyl, said phenyl, phenoxy or naphthyl groups being optionally substituted by one or more substituents selected from halogen, cyano, hydroxy, acyl, nitro, -SO<sub>2</sub>NH<sub>2</sub>, C<sub>1</sub>-C<sub>8</sub>-alkyl optionally substituted by C<sub>1</sub>-C<sub>8</sub>-alkoxy, C<sub>1</sub>-C<sub>8</sub>-haloalkyl, C<sub>1</sub>-C<sub>8</sub>-alkoxy, C<sub>1</sub>-C<sub>8</sub>-haloalkoxy, C<sub>1</sub>-C<sub>8</sub>-alkylthio, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>8</sub>-acylamino optionally substituted on the nitrogen atom by C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-alkylamino, aminocarbonyl, C<sub>1</sub>-C<sub>8</sub>-alkylamino-carbonyl, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)amino, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)aminocarbonyl, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)aminocarbonyl-methoxy,

or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 to 10 ring atoms of which 1, 2 or 3 are hetero atoms;

R<sup>4</sup> and R<sup>5</sup> are each independently hydrogen or C<sub>1</sub>-C<sub>8</sub>-alkyl, or R<sup>4</sup> is hydrogen and R<sup>5</sup> is hydroxy-C<sub>1</sub>-C<sub>8</sub>-alkyl, acyl, -SO<sub>2</sub>R<sup>8</sup> or -CON(R<sup>6</sup>)R<sup>7</sup>, or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached denote a 5- or 6-membered heterocyclic group;

R<sup>6</sup> and R<sup>7</sup> are each independently hydrogen or C<sub>1</sub>-C<sub>8</sub>-alkyl, or R<sup>6</sup> and R<sup>7</sup> together with the nitrogen atom to which they are attached denote a 5- or 6-membered heterocyclic group; and

R<sup>8</sup> is C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-haloalkyl, or phenyl optionally substituted by C<sub>1</sub>-C<sub>8</sub>-alkyl.

Terms used in the specification have the following meanings:

"C<sub>1</sub>-C<sub>8</sub>-alkyl" as used herein denotes straight chain or branched C<sub>1</sub>-C<sub>8</sub>-alkyl. Preferably, C<sub>1</sub>-C<sub>8</sub>-alkyl is C<sub>1</sub>-C<sub>4</sub>-alkyl.

"C<sub>3</sub>-C<sub>10</sub>-cycloalkyl" as used herein denotes cycloalkyl having 3 to 10 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, any of which can be substituted by one or more, usually one or two, C<sub>1</sub>-C<sub>4</sub>-alkyl groups, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Preferably C<sub>3</sub>-C<sub>10</sub>-cycloalkyl is C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, especially cyclopropyl.

"C<sub>1</sub>-C<sub>8</sub>-alkoxy" as used herein denotes straight chain or branched C<sub>1</sub>-C<sub>8</sub>-alkoxy. Preferably, C<sub>1</sub>-C<sub>8</sub>-alkoxy is C<sub>1</sub>-C<sub>4</sub>-alkoxy.

"C<sub>1</sub>-C<sub>8</sub>-haloalkyl" as used herein denotes C<sub>1</sub>-C<sub>8</sub>-alkyl as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms.

"C<sub>1</sub>-C<sub>8</sub>-haloalkoxy" as used herein denotes C<sub>1</sub>-C<sub>8</sub>-alkoxy as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms.

"Aminocarbonyl" as used herein denotes amino attached through the nitrogen atom to a carbonyl group.

"C<sub>1</sub>-C<sub>8</sub>-alkylamino" and "di(C<sub>1</sub>-C<sub>8</sub>-alkyl)amino" as used herein denote amino substituted respectively by one or two C<sub>1</sub>-C<sub>8</sub>-alkyl groups as hereinbefore defined, which may be the same or different. Preferably C<sub>1</sub>-C<sub>8</sub>-alkylamino and di(C<sub>1</sub>-C<sub>8</sub>-alkyl)amino are respectively C<sub>1</sub>-C<sub>4</sub>-alkylamino and di(C<sub>1</sub>-C<sub>4</sub>-alkyl)amino.

"C<sub>1</sub>-C<sub>8</sub>-alkylaminocarbonyl" and "di(C<sub>1</sub>-C<sub>8</sub>-alkyl)aminocarbonyl" as used herein denote aminocarbonyl as hereinbefore defined substituted respectively on the nitrogen atom by one or two C<sub>1</sub>-C<sub>8</sub>-alkyl groups as hereinbefore defined, which may be the same or different. Preferably C<sub>1</sub>-C<sub>8</sub>-alkylaminocarbonyl and di(C<sub>1</sub>-C<sub>8</sub>-alkyl)aminocarbonyl are respectively C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl and di(C<sub>1</sub>-C<sub>4</sub>-alkyl)aminocarbonyl.

"C<sub>1</sub>-C<sub>8</sub>-alkylthio" as used herein denotes C<sub>1</sub>-C<sub>8</sub>-alkyl as hereinbefore defined linked to -S-.

"Acyl" as used herein denotes alkylcarbonyl, for example C<sub>1</sub>-C<sub>8</sub>-alkylcarbonyl where C<sub>1</sub>-C<sub>8</sub>-alkyl may be one of the C<sub>1</sub>-C<sub>8</sub>-alkyl groups hereinbefore mentioned, optionally substituted by one or more halogen atoms; cycloalkylcarbonyl, for example C<sub>3</sub>-C<sub>8</sub>-cycloalkylcarbonyl where C<sub>3</sub>-C<sub>8</sub>-cycloalkyl may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; 5- or 6- membered heterocyclylcarbonyl having one or two hetero atoms selected from nitrogen, oxygen and sulfur in the ring, such as furylcarbonyl or pyridylcarbonyl; arylcarbonyl, for example C<sub>6</sub>-C<sub>10</sub>-arylcarbonyl such as benzoyl; or aralkylcarbonyl, for example C<sub>6</sub> to C<sub>10</sub>-aryl-C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl such as benzylcarbonyl or phenylethylcarbonyl. Preferably acyl is C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl.

"Acyloxy" as used herein denotes alkylcarbonyloxy, for example C<sub>1</sub>-C<sub>8</sub>-alkylcarbonyloxy where C<sub>1</sub>-C<sub>8</sub>-alkyl may be one of the C<sub>1</sub>-C<sub>8</sub>-alkyl groups hereinbefore mentioned, optionally substituted by one or more halogen atoms; cycloalkylcarbonyloxy, for example C<sub>3</sub>-C<sub>8</sub>-cycloalkylcarbonyloxy where C<sub>3</sub>-C<sub>8</sub>-cycloalkyl may be, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; 5- or 6- membered heterocyclylcarbonyloxy having one or two hetero atoms selected from nitrogen, oxygen and sulfur in the ring, such as furylcarbonyloxy or pyridylcarbonyloxy; arylcarbonyloxy, for example C<sub>6</sub>-C<sub>10</sub>-arylcarbonyloxy such as benzoyloxy; or aralkylcarbonyloxy, for example C<sub>6</sub> to C<sub>10</sub>-aryl-C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy such as benzylcarbonyloxy or phenylethylcarbonyloxy, or aryloxyalkylcarbonyloxy, for example, C<sub>6</sub>-C<sub>10</sub>-aryloxy-C<sub>1</sub>-C<sub>8</sub>-alkylcarbonyloxy, any of which is optionally substituted in the aryl moiety by at least one substituent selected from C<sub>1</sub>-C<sub>8</sub>-alkoxy, halogen, C<sub>1</sub>-C<sub>8</sub>-alkylcarbonyl, aminosulfonyl, C<sub>1</sub>-C<sub>8</sub>-alkylaminosulfonyl and di(C<sub>1</sub>-C<sub>8</sub>-alkyl)aminosulfonyl. Preferably acyloxy is C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy, or benzoyloxy or

phenoxy-C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyloxy optionally substituted in the benzene ring thereof by at least one substituent selected from C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl or aminosulfonyl.

"Acylamino" as used herein denotes amino substituted by acyl as hereinbefore defined.

"Halogen" as used herein may be fluorine, chlorine, bromine or iodine; preferably it is fluorine, chlorine or bromine.

"C<sub>1</sub>-C<sub>8</sub>-alkoxycarbonyl" as used herein denotes C<sub>1</sub>-C<sub>8</sub>-alkoxy as hereinbefore defined attached through the oxygen atom to a carbonyl group.

"Di-(C<sub>1</sub>-C<sub>8</sub>-alkyl)aminocarbonylmethoxy" as used herein denotes aminocarbonylmethoxy disubstituted on the amino nitrogen atom by C<sub>1</sub>-C<sub>8</sub>-alkyl as hereinbefore defined, the two C<sub>1</sub>-C<sub>8</sub>-alkyl groups being the same or different.

"Optionally substituted" means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

In Ar, the phenyl group may be substituted, for example by one, two or three, preferably one or two halogen atoms, preferably selected from fluorine and chlorine atoms, or by one or two C<sub>1</sub>-C<sub>8</sub>-alkyl, cyano or nitro groups, or by C<sub>1</sub>-C<sub>8</sub>-alkyl and one or two halogen, preferably fluorine or chlorine, atoms. When there is one halogen substituent, it is preferably para to the indicated group X. When there are two or three halogen substituents, preferably one is para to the indicated group X and at least one of the others is ortho to the para-halogen substituent.

R<sup>3</sup> as substituted phenyl may, for example, be substituted by one, two, three, four or five, preferably by one, two or three, of the abovementioned substituents. R<sup>3</sup> may be, for example, phenyl substituted by one, two or three substituents selected from halogen, cyano, hydroxy, nitro, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>4</sub>-haloalkoxy, -CO-NH<sub>2</sub>, di(C<sub>1</sub>-C<sub>4</sub>-alkyl)aminocarbonylmethoxy, C<sub>1</sub>-C<sub>4</sub>-alkyl optionally substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-haloalkyl, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkylthio, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl, di(C<sub>1</sub>-C<sub>4</sub>-alkyl)amino, C<sub>1</sub>-C<sub>4</sub>-alkylaminocarbonyl or C<sub>1</sub>-C<sub>4</sub>-alkyl-carbonylamino. R<sup>3</sup> as substituted phenyl is preferably phenyl substituted by one or more substituents selected from cyano, halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl optionally substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkylcarbonyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkoxycarbonyl, -CO-NH<sub>2</sub>, -SO<sub>2</sub>-NH<sub>2</sub>, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkyl-

aminocarbonyl, di(C<sub>1</sub>-C<sub>4</sub>-alkyl)aminocarbonyl-methoxy or C<sub>1</sub>-C<sub>4</sub>-alkyl-carbonylamino, especially cyanophenyl, particularly meta-cyanophenyl, and disubstituted phenyl where one substituent is C<sub>1</sub>-C<sub>4</sub>-alkoxy or di(C<sub>1</sub>-C<sub>4</sub>-alkyl)aminocarbonylmethoxy, preferably ortho to the bond linking R<sup>3</sup> to the remainder of the molecule shown in formula I, and the other, preferably para to the C<sub>1</sub>-C<sub>4</sub>-alkoxy group, is C<sub>1</sub>-C<sub>4</sub>-alkoxy, halogen, cyano or C<sub>1</sub>-C<sub>4</sub>-alkyl.

When R<sup>3</sup> is C<sub>1</sub>-C<sub>4</sub>-alkyl substituted by optionally substituted phenoxy, the substituent(s) on phenoxy may be, for example, one, two or three substituents selected from halogen, cyano, C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-alkoxy or C<sub>1</sub>-C<sub>8</sub>-alkylcarbonyl.

R<sup>3</sup> as a heterocyclic group may be, for example, a group having 5 to 11 ring atoms of which one, two, three or four, preferably one or two, are hetero atoms selected from nitrogen, oxygen or sulfur, such as pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyranyl, pyrazinyl, or a 5-, 6- or 7-membered heterocyclic, ring preferably having one or two oxygen or nitrogen ring atoms, fused to a benzene ring, said heterocyclic group being optionally substituted by substituents including halogen, C<sub>1</sub>-C<sub>4</sub>-alkyl optionally substituted by C<sub>1</sub>-C<sub>4</sub>-alkoxy, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>3</sub>-C<sub>10</sub>-cycloalkyl, phenyl, phenyl-C<sub>1</sub>-C<sub>4</sub>-alkyl and C<sub>2</sub>-C<sub>4</sub>-alkynyl. Preferably a heterocyclic group having 5 to 11 ring atoms of which one, two, three or four, preferably one or two, are hetero atoms selected from nitrogen, oxygen or sulphur is a heterocyclic group having 5, 6 or 7 ring atoms of which one, two, three or four, are hetero atoms selected from nitrogen, oxygen and sulphur. It is especially preferred that the heterocyclic group is thiadiazolyl, pyrazolyl, tetrazolyl or isoxazolyl, optionally substituted by one or more of C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy and C<sub>3</sub>-C<sub>6</sub>-cycloalkyl.

R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached as a heterocyclic group may be, for example, a group having a 5- or 6-membered ring of which one, two or three are heteroatoms, optionally fused to a benzene ring, such as piperidinyl, piperazinyl, morpholino, or benzopiperidinyl, optionally substituted by one or more substituents including C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-alkoxy, C<sub>3</sub>-C<sub>10</sub>-cycloalkyl and halogen.

R<sup>1</sup> as optionally substituted C<sub>1</sub>-C<sub>8</sub>-alkyl is preferably optionally substituted C<sub>1</sub>-C<sub>4</sub>-alkyl, especially C<sub>1</sub>-C<sub>4</sub>-alkyl or substituted methyl or ethyl. When R<sup>1</sup> is substituted by a cyclic organic group, the latter may be a carbocyclic or heterocyclic group, for example a C<sub>3</sub>-C<sub>15</sub>-carbocyclic group or a 5- to 7-membered heterocyclic group having one or more, preferably one, two or three, ring hetero atoms selected from nitrogen, oxygen and sulfur. The C<sub>3</sub>-C<sub>15</sub>-carbocyclic



group may be, for example, a cycloaliphatic group having 3 to 8 carbon atoms, preferably C<sub>5</sub> - or C<sub>6</sub> - cycloalkyl such as cyclopentyl, methylcyclopentyl or cyclohexyl. The C<sub>3</sub>-C<sub>15</sub>-carbocyclic group may alternatively be, for example, a C<sub>6</sub>-C<sub>15</sub> aromatic group, such as phenyl, which is unsubstituted or substituted by C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-alkoxy, halogen, cyano, -CON(R<sup>4</sup>)R<sup>5</sup>, -SO<sub>2</sub>N(R<sup>4</sup>)R<sup>5</sup> or C<sub>1</sub>-C<sub>8</sub>-alkylsulfonylamino where R<sup>4</sup> and R<sup>5</sup> are as hereinbefore defined. The heterocyclic group may have one nitrogen, oxygen or sulfur atom in the ring or it may have two nitrogens, or one oxygen and one or two nitrogens, or one sulfur and one or two nitrogens in the ring. The heterocyclic group is preferably a heterocyclic aromatic group, especially a 5- or 6- membered heterocyclic group such as furyl, imidazolyl, thiazolyl or pyridyl. Preferred embodiments include those in which R<sup>1</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub>-alkyl substituted by hydroxy or C<sub>1</sub>-C<sub>4</sub>-alkoxy.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Preferred compounds of the present invention include compounds of formula I in free or salt form, wherein

Ar is phenyl substituted by halo;

X is -S-, -S(=O)- or -S(=O)<sub>2</sub>-;

m is 2;

R<sup>1</sup> is C<sub>1</sub>-C<sub>8</sub>-alkyl optionally substituted by hydroxy or C<sub>1</sub>-C<sub>8</sub>-alkoxy;

Y is oxygen;

R<sup>2</sup> is hydrogen; and

R<sup>3</sup> is a heterocyclic group having 5 to 11 ring atoms of which 1 to 4 are hetero atoms.

Especially preferred compounds of the present invention include compounds of formula I in free or salt form, wherein

Ar is phenyl substituted by halo, preferably chloro;

X is -S-, -S(=O)- or -S(=O)<sub>2</sub>-;

m is 2;

R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub>-alkyl optionally substituted by hydroxy or C<sub>1</sub>-C<sub>4</sub>-alkoxy;

Y is oxygen;

R<sup>2</sup> is hydrogen; and

R<sup>3</sup> is a heterocyclic group having 5, 6 or 7 ring atoms of which one, two, three or four, are hetero atoms selected from nitrogen, oxygen and sulphur, said heterocyclic group being optionally substituted by C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy or C<sub>3</sub>-C<sub>6</sub>-cycloalkyl.

The compounds represented by formula I are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxynaphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures.

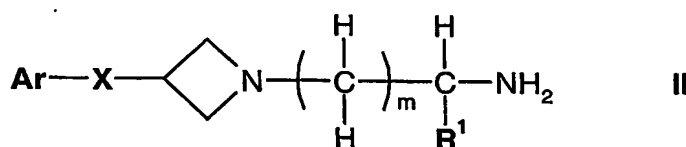
Compounds of formula I which contain acidic, e.g. carboxyl, groups, are also capable of forming salts with bases, in particular pharmaceutically acceptable bases such as those well known in the art; suitable such salts include metal salts, particularly alkali metal or alkaline earth metal salts such as sodium, potassium, magnesium or calcium salts, or salts with ammonia or pharmaceutically acceptable organic amines or heterocyclic bases such as ethanolamines, benzylamines or pyridine. These salts may be prepared from compounds of formula I by known salt-forming procedures.

When R<sup>1</sup> is other than hydrogen, the carbon atom to which R<sup>1</sup> is attached in formula I is asymmetric, in which case the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. When X is -S(=O), the sulfur atom is asymmetric, so again the compounds exist in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. In both cases the invention embraces both individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

Specific especially preferred compounds of the invention are those described hereinafter in the Examples.

The invention also provides a process for the preparation of compounds of formula I which comprises

- (i) (A) for the preparation of compounds of formula I where  $R^2$  is hydrogen, reacting a compound of formula II

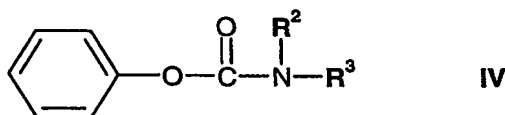


or a protected form thereof, where Ar, X, m and  $R^1$  are as hereinbefore defined, with a compound of formula III



where Y and  $R^3$  are as hereinbefore defined; or

- (B) for the preparation of compounds of formula I where Y is oxygen, reacting a compound of formula II where Ar, X, m and  $R^1$  are as hereinbefore defined, with a compound of formula IV



where  $R^2$  and  $R^3$  are as hereinbefore defined; or

- (C) for the preparation of compounds of formula I where X is  $-\text{S}(=\text{O})_2-$ , oxidising a compound of formula I in protected form where X is  $-\text{S}-$  and Ar, m,  $R^1$ , Y,  $R^2$  and  $R^3$  are hereinbefore defined; and

- (ii) recovering the product in free or salt form.

Process variant (A) may be effected using known procedures for reaction of amines with isocyanates or analogously e.g. as hereinafter described in the Examples. The reaction is conveniently carried out in an organic solvent, for example a halohydrocarbon such as dichloromethane (DCM) or an ether such as dioxane. The reaction temperature may be e.g. from 0 °C to 100 °C, conveniently ambient temperature.

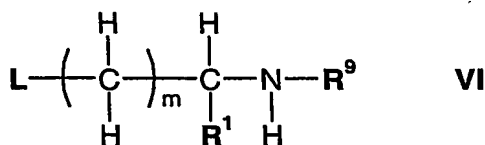
Process variant (B) may be effected using known procedures for reaction of amines with carbamic acid phenyl esters or analogously e.g. as hereinafter described in the Examples. The reaction is conveniently carried out in an organic solvent such as dimethyl sulfoxide (DMSO). The reaction temperature may be e.g. from 20 to 100 °C, conveniently ambient temperature.

Process variant (C) may be effected using known procedures for oxidising sulfanyl groups to form sulfonyl groups or analogously e.g. as hereinafter described in the Examples. The oxidising agent used is preferably a perbenzoic acid, especially meta chloro-per-benzoic acid. The reaction is conveniently carried out in an organic solvent such as dichloromethane (DCM). The reaction temperature may be e.g. from 5 to 25 °C, preferably about 15 °C.

Compounds of formula II may be prepared by reacting a compound of formula V



where Ar and X are as hereinbefore defined, with a compound of formula VI



where L is a halogen, preferably bromine or iodo, and R<sup>1</sup> and m are as hereinbefore defined, with the proviso that when R<sup>1</sup> contains a reactive functional group such as a hydroxy group, the reactive group may be in protected form, for example a hydroxy group protected as a tert-butoxy group, and R<sup>9</sup> is hydrogen or an amine-protective group, for example a tert-butoxy-carbonyl group, and, where R<sup>9</sup> is a protective group, replacing R<sup>9</sup> in the product by hydrogen, and, where R<sup>1</sup> in the product contains a protected functional group, replacing the protecting group with hydrogen, or analogously e.g. as hereinafter described in the Examples. When R<sup>9</sup> is hydrogen, reaction between a compound of formula VI and a salt of a compound of formula V may be effected by the procedures described in US patent specification 4559349. When R<sup>9</sup> is a protective group, reaction between compounds of formulae V and VI may be effected using known methods, for example in the presence of a tertiary organic base such as triethylamine or 1,8-diaza-bicyclo-[5.4.0]undec-7-ene (DBU), conveniently in an inert organic solvent, for example a polar solvent such as dimethylformamide, the reaction temperature suitably being from 0 to 40°C, preferably ambient temperature. Replacement of a protective group R<sup>9</sup> by hydrogen may be effected using known procedures; for example, where R<sup>9</sup> is tert-butoxy-carbonyl, by treatment with a carboxylic acid such as trifluoroacetic acid. Replacement of a

protecting group in  $R^1$  may be affected using known procedures, for example, when  $R^1$  contains a hydroxy group protected as an ether group, such as tert-butoxy, by treatment with HBr in a carboxylic acid such as acetic acid; when  $R^9$  is a protective group, this treatment also replaces  $R^9$  by hydrogen.

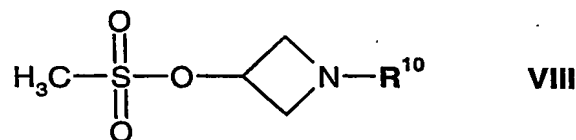
Where reference is made herein to protected functional groups or to protecting groups, the protecting groups may be chosen in accordance with the nature of the functional group, for example as described in *Protective Groups in Organic Synthesis*, T. W. Greene, P.G.M. Wuts, John Wiley & Sons Inc, Third Edition, 1999, which reference also describes procedures suitable for replacement of the protecting groups by hydrogen.

Compounds of formula III are commercially available or may be prepared by known methods. Compounds of formula IV are known or may be prepared by known procedures or analogously e.g. as hereinafter described in the Examples.

Compounds of formula V where X is -S- may be prepared by reacting a compound of formula VII



where Ar is as hereinbefore defined, with a compound of formula VIII



in the presence of sodium hydride where  $R^{10}$  is a protecting group, and replacing  $R^{10}$  in the product by hydrogen, or analogously e.g. as hereinafter described in the Examples. The reaction may be carried out in an inert organic solvent such as dimethylformamide (DMF). Suitable reaction temperatures may be from 20°C to 150°C, conveniently from 50 to 70°C. The replacement of  $R^{10}$  by hydrogen may be effected using known procedures or analogously e.g. as hereinafter described in the Examples.

Compounds of formula V where X is -S(=O)- may be prepared by reacting the corresponding aryl-sulfanyl-azetidine, preferably a protected form thereof, with an oxidising agent such as a per-benzoic acid, or analogously e.g. as hereinafter described in the Examples. The reaction is conveniently carried out in an organic solvent such as dichloromethane (DCM). The reaction temperature may be e.g. from 5 to 25 °C, preferably about 15 °C.

Compounds of formula V where X is  $-S(=O)_2-$  may be prepared by reacting the corresponding aryl-sulfanyl-azetidine, preferably a protected form thereof, with an oxidising agent such as a per-benzoic acid, or analogously e.g. as hereinafter described in the Examples. The reaction is conveniently carried out in an organic solvent such as dichloromethane (DCM). The reaction temperature may be e.g. from 5 to 25 °C, preferably about 15 °C.

Compounds of formulae VI, VII or VIII are known or may be prepared by known procedures or analogously e.g. as hereinafter described in the Examples.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallization. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallization or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Compounds of formula I in free or pharmaceutically acceptable salt form, hereinafter referred to alternatively as agents of the invention, are useful as pharmaceuticals. Accordingly the invention also provides a compound of formula I in free or pharmaceutically acceptable salt form for use as a pharmaceutical. The agents of the invention act as CCR-3 receptor antagonists, thereby inhibiting the infiltration and activation of inflammatory cells, particularly eosinophils, and inhibiting allergic response. The inhibitory properties of agents of the invention can be demonstrated in the following assay:

In this assay the effect of agents of the invention on the binding of human eotaxin to human CCR-3 is determined. Recombinant cells expressing human CCR-3 are captured by wheatgerm agglutinin (WGA) polyvinyltoluidene (PVT) SPA beads (available from Amersham), through a specific interaction between the WGA and carbohydrate residues of glycoproteins on the surface of the cells.  $[^{125}\text{I}]$ -human eotaxin (available from Amersham) binds specifically to CCR-3 receptors bringing the  $[^{125}\text{I}]$ -human eotaxin in close proximity to the SPA beads. Emitted  $\alpha$ -particles from the  $[^{125}\text{I}]$ -human eotaxin excite, by its proximity, the fluorophore in the beads and produce light. Free  $[^{125}\text{I}]$ -human eotaxin in solution is not in close proximity to the scintillant and hence does not produce light. The scintillation count is therefore a measure of the extent to which the test compound inhibits binding of the eotaxin to the CCR-3.

Preparation of Assay Buffer: 5.96 g HEPES and 7.0 g sodium chloride are dissolved in distilled water and 1M aqueous  $\text{CaCl}_2$  (1 ml) and 1M aqueous  $\text{MgCl}_2$  (5 ml) are added. The pH is adjusted to 7.6 with NaOH and the solution made to a final volume of 1 L using distilled water. 5 g bovine serum albumin and 0.1 g sodium azide are then dissolved in the solution and the resulting buffer stored at 4°C. A Complete™ protease inhibitor cocktail tablet (available from Boehringer) is added per 50 ml of the buffer on the day of use.

Preparation of Homogenisation Buffer: Tris-base (2.42 g) is dissolved in distilled water, the pH of the solution is adjusted to 7.6 with hydrochloric acid and the solution is diluted with distilled water to a final volume of 1 l. The resulting buffer is stored at 4°C. A Complete™ protease inhibitor cocktail tablet is added per 50 ml of the buffer on the day of use.

Preparation of membranes: Confluent rat basophil leukaemia (RBL-2H3) cells stably expressing CCR3 are removed from tissue culture flasks using enzyme-free cell dissociation buffer and resuspended in phosphate-buffered saline. The cells are centrifuged (800 g, 5 minutes), the pellet resuspended in ice-cold homogenisation buffer using 1 ml homogenisation buffer per gram of cells and incubated on ice for 30 minutes. The cells are homogenised on ice with 10 strokes in a glass mortar and pestle. The homogenate is centrifuged (800 g, 5 minutes, 4°C), the supernatant further centrifuged (48,000 g, 30 minutes, 4°C) and the pellet redissolved in Homogenisation Buffer containing 10% (v/v) glycerol. The protein content of the membrane preparation is estimated by the method of Bradford (Anal. Biochem. (1976) 72:248) and aliquots are snap frozen and stored at -80°C.

The assay is performed in a final volume of 250 µl per well of an Optiplate™ microplate (ex Canberra Packard). To selected wells of the Optiplate™ are added 50 µl of solutions of a test compound in Assay Buffer containing 5 % DMSO (concentrations from 0.01 nM to 10 µM). To determine total binding, 50 µl of the Assay Buffer containing 5 % DMSO is added to other selected wells. To determine non-specific binding, 50 µl of 100 nM human eotaxin (ex R&D Systems) in Assay Buffer containing 5 % DMSO is added to further selected wells. To all wells are added 50 µl [ $^{125}\text{I}$ ]-Human eotaxin (ex Amersham) in Assay Buffer containing 5 % DMSO at a concentration of 250 pM (to give a final concentration of 50 pM per well), 50 µl of WGA-PVT SPA beads in Assay Buffer (to give a final concentration of 1.0 mg beads per well) and 100 µl of the membrane preparation at a concentration of 100 µg protein in Assay Buffer (to give a final concentration of 10 µg protein per well). The plate is then incubated for 4 hours at room temperature. The plate is sealed using TopSeal-S™ sealing tape (ex Canberra Packard)

according to the manufacturer's instructions. The resulting scintillations are counted using a Canberra Packard TopCount™ scintillation counter, each well being counted for 1 minute. The concentration of test compound at which 50% inhibition occurs (IC<sub>50</sub>) is determined from concentration-inhibition curves in a conventional manner.

The compounds of the Examples hereinbelow generally have IC<sub>50</sub> values below 1 μM in the above assay. For instance, the compounds of Examples 1, 19 and 25 have IC<sub>50</sub> values of 0.278, 0.002 and 0.820 μM respectively.

Most of the compounds of the Examples exhibit selectivity for inhibition of CCR-3 binding relative to inhibition of binding of the alpha-1 adrenergic receptor. Some of the compounds e.g. that of Example 19], are also histamine H1 antagonists.

The inhibitory properties of agents of the invention on binding of the alpha-1 adrenergic receptor can be determined in the following assay:

Cerebral cortices from male Sprague-Dawley rats (175-200 g) are dissected and homogenised in 10 volumes of ice cold 0.32 M sucrose (containing 1 mM MgCl<sub>2</sub> dihydrate and 1mM K<sub>2</sub>HPO<sub>4</sub>) with a glass/Teflon homogeniser. The membranes are centrifuged at 1000 x g for 15 min, the pellet discarded and the centrifugation repeated. The supernatants are pooled and centrifuged at 18,000 x g for 15 minutes. The pellet is osmotically shocked in 10 volumes of water and kept on ice for 30 minutes. The suspension is centrifuged at 39,000 x g for 20 minutes, resuspended in Krebs-Henseleit buffer pH 7.4 (1.17 mM MgSO<sub>4</sub> anhydrous, 4.69 mM KCl, 0.7 mM K<sub>2</sub>HPO<sub>4</sub> anhydrous, 0.11 M NaCl, 11 mM D-glucose and 25 mM NaHCO<sub>3</sub>) containing 20 mM Tris, and kept for 2 days at -20°C. The membranes are then thawed at 20-23°C, washed three times with Krebs-Henseleit buffer by centrifugation at 18,000 x g for 15 minutes, left overnight at 4°C and washed again three times. The final pellet is resuspended with a glass/Teflon homogeniser in 125 ml/100 membranes in the same buffer. A sample is taken to determine the protein concentration (using the Bradford Assay with gamma globulin as the standard) and the remainder aliquoted and stored at -80°C.

The resulting membranes are subjected to a radioligand binding assay. The assay is conducted in triplicate using 96 well plates containing [125I]-HEAT (Amersham) (40 pM, K<sub>d</sub>: 58.9 ± 18.7 pM), unlabelled test compound and membrane (57.1 μg/ml) to yield a final volume of 250 μl (assay buffer containing 50 mM Tris-base and 0.9% (w/v) NaCl, pH 7.4). The plates are



incubated at 37°C for 60 minutes, after which rapid vacuum filtration over Whatman™ GF/C 96 well filter plates is carried out. Each plate is then washed three times with 10ml of ice cold assay buffer using a Brandel Cell harvester (Gaithersburg, MD). Following drying of the plates for 3 h. at 50°C, 40 µl of Microscint 20 is added to each well, the plates incubated at room temperature for a further 20 minutes and the retained radioactivity quantified in a Packard TopCount NXT™ scintillation counter.

Stock solutions of test compounds are dissolved initially in 100 % DMSO and diluted with assay buffer to the required concentrations to yield 1 % (v/v) DMSO. The concentration of test compound at which 50% inhibition occurs (IC<sub>50</sub>) is determined from concentration-inhibition curves in a conventional manner.

Having regard to their inhibition of binding of CCR-3, agents of the invention are useful in the treatment of conditions mediated by CCR-3, particularly inflammatory or allergic conditions. Treatment in accordance with the invention may be symptomatic or prophylactic.

Accordingly, agents of the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, bronchial hyperreactivity, remodelling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial or viral infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be

apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant from any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), acute/adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, e.g., acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

Having regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, agents of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Löffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

Agents of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphigus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

Agents of the invention may also be used for the treatment of other diseases or conditions, in particular diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, e.g. atrophic, chronic, or seasonal rhinitis, inflammatory conditions of the gastrointestinal tract, for example inflammatory bowel disease such as ulcerative colitis and Crohn's disease, diseases of the bone and joints including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and systemic sclerosis, and other diseases such as atherosclerosis, multiple sclerosis, diabetes (type I), myasthenia gravis, hyper IgE syndrome and acute and chronic allograft rejection, e.g. following transplantation of heart, kidney, liver, lung or bone marrow.

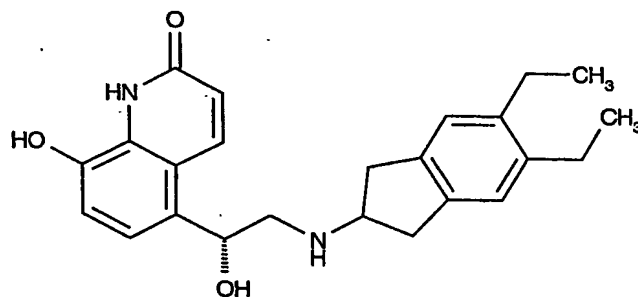
The effectiveness of an agent of the invention in inhibiting inflammatory conditions, for example in inflammatory airways diseases, may be demonstrated in an animal model, e.g. a mouse or rat model, of airways inflammation or other inflammatory conditions, for example as described by Szarka et al, J. Immunol. Methods (1997) 202:49-57; Renzi et al, Am. Rev. Respir. Dis. (1993) 148:932-939; Tsuyuki et al., J. Clin Invest. (1995) 96:2924-2931; and Cernadas et al (1999) Am. J. Respir. Cell Mol. Biol. 20:1-8.

The agents of the invention are also useful as co-therapeutic agents for use in combination with other drug substances such as anti-inflammatory, bronchodilatory or antihistamine drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the other drug substance in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the other drug substance.

Such anti-inflammatory drugs include steroids, in particular gluco-corticosteroids such as budesonide, beclamethasone, fluticasone, ciclesonide or mometasone, LTB4 antagonists such as those described in US 5451700, LTD4 antagonists such as montelukast and zafirlukast, dopamine receptor agonists such as cabergoline, bromocriptine, ropinirole and 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]-amino]ethyl]-2(3H)-benzothiazolone and pharmaceutically acceptable salts thereof (the hydrochloride being Viozan® - AstraZeneca), and PDE4 inhibitors such as Ariflo® (GlaxoSmithKline), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall

Prodesfarma), PD189659 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene) and KW-4490 (Kyowa Hakko Kogyo) and A2a agonists such as those described in EP 1052264, EP 1241176, WO 0023457, WO0077018, WO 0123399, WO 0160835, WO 0194368, WO 0200676, WO 0222630, WO 0296462, WO 0127130, WO 0127131, WO 9602543, WO 9602553, WO 9828319, WO 9924449, WO 9924450, WO 9924451, WO 9938877, WO 9941267, WO 9967263, WO 9967264, WO 9967265, WO 9967266, WO 9417090, EP 409595A2 and WO 0078774 and A2b antagonists such as those described in WO 02/42298.

Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide, but also those described in EP 424021, US 5171744 (Pfizer) and WO 01/04118 (Almirall Prodesfarma), and beta-2 adrenoceptor agonists such as salbutamol, terbutaline, salmeterol and, especially, formoterol and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of PCT International Publication No. WO 00/75114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof.

Co-therapeutic antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride. Combinations of agents of the invention and steroids, beta-2 agonists, PDE4 inhibitors or LTD4 antagonists may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents, PDE4 inhibitors, dopamine receptor agonists or LTB4 antagonists may be used, for example, in the treatment of asthma or, particularly, COPD.

Other useful combinations of agents of the invention with anti-inflammatory drugs are those with other antagonists of chemokine receptors, e.g. CCR-1, CCR-2, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-9 and CCR10, CXCR1, CXCR2, CXCR3, CXCR4, CXCR5,

particularly CCR-5 antagonists such as Schering-Plough antagonists SC-351125, SCH-55700 and SCH-D, Takeda antagonists such as N-[[4-[[[6,7-dihydro-2-(4-methylphenyl)-5H-benzocyclohepten-8-yl]carbonyl]amino]phenyl]-methyl]tetrahydro-N,N-dimethyl-2H-pyran-4-aminium chloride (TAK-770), CCR-5 antagonists described in US 6166037 (particularly claims 18 and 19), WO 00/66558 (particularly claim 8), and WO 00/66559 (particularly claim 9).

In accordance with the foregoing, the invention also provides a method for the treatment of a condition mediated by CCR-3, for example an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease, which comprises administering to a subject, particularly a human subject, in need thereof an effective amount of a compound of formula I in a free or pharmaceutically acceptable salt form as hereinbefore described. In another aspect the invention provides the use of a compound of formula I, in free or pharmaceutically acceptable salt form, as hereinbefore described for the manufacture of a medicament for the treatment of a condition mediated by CCR-3, for example an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; by inhalation, for example in the treatment of inflammatory or obstructive airways disease; intranasally, for example in the treatment of allergic rhinitis; topically to the skin, for example in the treatment of atopic dermatitis; or rectally, for example in the treatment of inflammatory bowel disease.

In a further aspect, the invention also provides a pharmaceutical composition comprising as active ingredient a compound of formula I in free or pharmaceutically acceptable salt form, optionally together with a pharmaceutically acceptable diluent or carrier therefor. The composition may contain a co-therapeutic agent such as an anti-inflammatory bronchodilatory or antihistamine drug as hereinbefore described. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

When the composition comprises an aerosol formulation, it preferably contains, for example, a hydro-fluoro-alkane (HFA) propellant such as HFA134a or HFA227 or a mixture of these, and may contain one or more co-solvents known in the art such as ethanol (up to 20% by weight), and/or one or more surfactants such as oleic acid or sorbitan trioleate, and/or one or more bulking agents such as lactose. When the composition comprises a dry powder formulation, it preferably contains, for example, the compound of formula I having a particle diameter up to 10 microns, optionally together with a diluent or carrier, such as lactose, of the desired particle size distribution and a compound that helps to protect against product performance deterioration due to moisture. When the composition comprises a nebulised formulation, it preferably contains, for example, the compound of formula I either dissolved, or suspended, in a vehicle containing water, a co-solvent such as ethanol or propylene glycol and a stabiliser, which may be a surfactant.

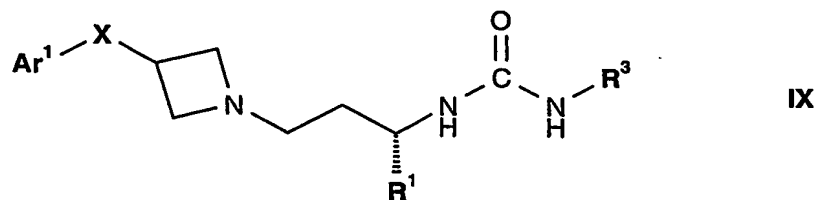
The invention includes (A) an agent of the invention in inhalable form, e.g. in an aerosol or other atomisable composition or in inhalable particulate, e.g. micronised form, (B) an inhalable medicament comprising an agent of the invention in inhalable form; (C) a pharmaceutical product comprising such an agent of the invention in inhalable form in association with an inhalation device; and (D) an inhalation device containing an agent of the invention in inhalable form.

Dosages of agents of the invention employed in practising the present invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of 0.01 to 30 mg/kg while for oral administration suitable daily doses are of the order of 0.01 to 100 mg/kg.

The invention is illustrated by the following Examples.

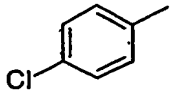
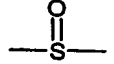
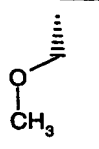
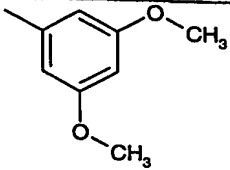
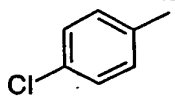

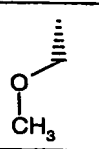
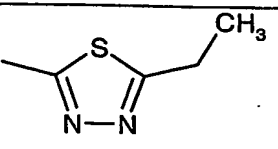
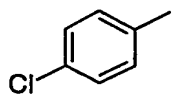

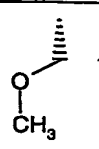
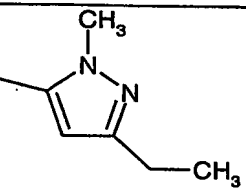
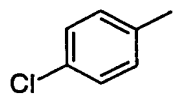
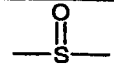
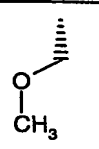
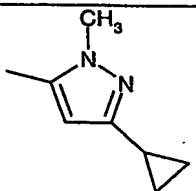
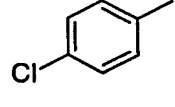
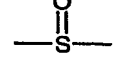
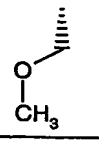
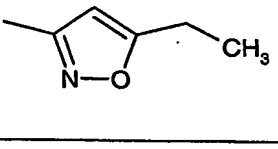
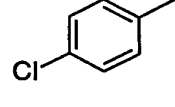
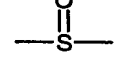
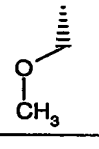
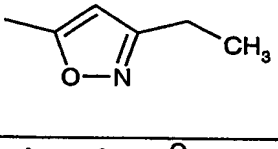
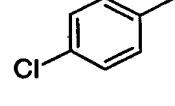
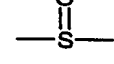

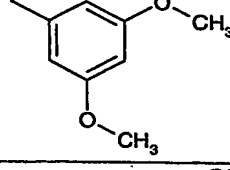
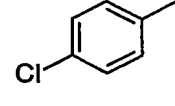
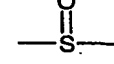

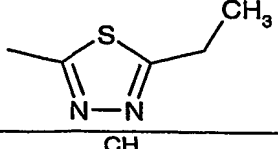
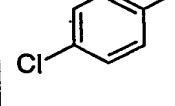
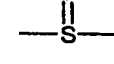

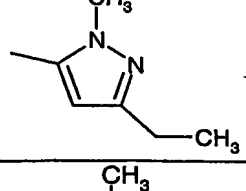
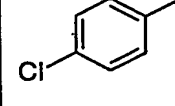
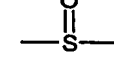

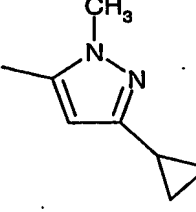
**EXAMPLES**

Compounds of formula I that are also formula IX



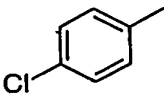
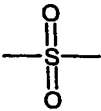

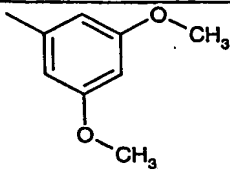
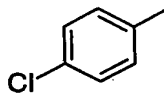
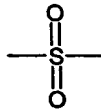

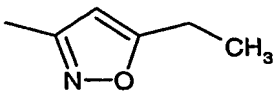
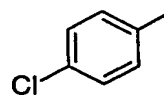
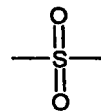

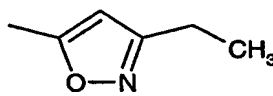
where Ar, X and R<sup>3</sup> are as shown in the following table, the methods of preparation being described hereinafter. The table also shows characterising mass spectrometry data. The compounds are all in free form.

Ex.	Ar	X	R <sup>1</sup>	R <sup>3</sup>	MS [M+H]
1					484.32
2					458.08
3					-
4					466.18
5					-
6					-

7					-
8					-
9					-
10					-
11					-
12					-
13					-
14					-
15					-
16					-



17					-
18					-
19					442.07
20					-
21					-
22					-
23					-
24					-
25					474.11
26					-
27					-

28					-
29					-
30					-

### Preparation of Intermediates

#### [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester:

#### (S)-3-tert-Butoxycarbonylamino-4-(tert-butyl-diphenyl-silanyloxy)-butyric acid benzyl ester

A solution of (S)-3-tert-butoxycarbonylamino-4-hydroxy-butyric acid benzyl ester (1.34 g, 4.37 mmol) (prepared using the method of Rodriguez, Marc; Linares, Muriel; Doulut, Sylvie; Heitz, Annie; Martinez, Jean; Tetrahedron Lett. (1991), 32(7), 923-6. ) and imidazole (0.88 g, 13.01 mmol in dimethylformamide (7 ml) is treated with tertbutyldiphenylsilyl chloride (1.69 ml, 6.5 mmol). The reaction mixture is stirred together at room temperature for 1 hour, then diluted with water and extracted into ethyl acetate. The ethyl acetate phase is dried over MgSO<sub>4</sub> and evaporated. The crude product is purified by flash silica chromatography (elution with 1:1 ethyl acetate/hexane) to afford (S)-3-tert-butoxycarbonylamino-4-(tert-butyl-diphenyl-silanyloxy)-butyric acid benzyl ester. [M-BOC] 448.0.

#### [(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-hydroxy-propyl]-carbamic acid tert-butyl ester

A solution of (S)-3-tert-butoxycarbonylamino-4-(tert-butyl-diphenyl-silanyloxy)-butyric acid benzyl ester in (2.37 g, 4.33 mmol) in dry diethylether (25 ml) at 0°C is treated with a 2 M solution of lithium borohydride in THF (4.33 ml). The reaction mixture is allowed to warm to ambient temperature and stirred for 3 hours under argon, then quenched by addition of water (10 ml) and 0.5 M aqueous citric acid solution (20 ml). The ether is separated, and the aqueous phase extracted with more ether. The combined ether phases are dried over MgSO<sub>4</sub> and evaporated. The crude product is purified by flash silica chromatography on a biotage column

(90 g) (elution with a 1:3 ethyl acetate/hexane then methanol ) to afford [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-hydroxy-propyl]-carbamic acid tert-butyl ester [M-BOC] 344.1.

[(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester

A suspension of polystyrene resin-bound triphenylphosphine (2.33 g, 3 mmol/g) in dry dichloromethane (25 ml) is treated with iodine (1.56 g, 6.16 mmol) and stirred for 15 minutes under argon . Imidazole (0.477 g, 7.0 mmol) is added and the reaction mixture stirred at room temperature for a further 15 minutes. The reaction mixture is then treated with a solution of [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-hydroxy-propyl]-carbamic acid tert-butyl ester (1.24 g, 2.8 mmol) in dichloromethane (5 ml). The reaction mixture is refluxed for 2 hours under argon, then filtered through a Celite™ filter pad, washing with dichloromethane. The filtrate is washed with 5% aqueous sodium thiosulphate solution and water, dried over MgSO<sub>4</sub> and evaporated. The crude product is purified by flash silica chromatography (elution with 1:99 methanol/dichloromethane) to afford [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester. [M-BOC] 453.9.

[(S)-3-Iodo-1-methoxymethyl-propyl]-carbamic acid tert-butyl ester:

(S)-3-tert-Butoxycarbonylamino-4-methoxy-butyric acid benzyl ester

A solution of (S)-3-tert-butoxycarbonylamino-4-hydroxy-butyric acid benzyl ester (31.4 g, 101 mmol) (prepared using the method of Rodriguez, Marc; Linares, Muriel; Doulut, Sylvie; Heitz, Annie; Martinez, Jean ;Tetrahedron Lett. (1991), 32(7), 923-6. ) in dichloromethane (280 ml) is cooled to -20°C and a 48% aqueous solution of tetrafluoroboric acid ( 13.3 ml, 101 mmol) added. With vigorous stirring is added dropwise a 2.0 M solution of trimethylsilyl-diazomethane (50.8 ml, 101 mmol) ) in hexane over 35 minutes. After stirring for a further 30 minutes, a second aliquot of trimethylsilyldiazomethane is added (12.7 ml, 25 mmol) slowly over 10 minutes. After stirring for a further 30 minutes at -20°C a further aliquot of trimethylsilyl-diazomethane (12.7 ml, 25 mmol) is added over 10 minutes. This pattern is continued until a total of 127 ml of trimethylsilyldiazomethane solution (254 mmol) is added. After the last addition the reaction mixture is left to stir for 1.5 hours at -20°C. The reaction mixture is then quenched with water and extracted into dichloromethane. The organic phase is dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution with 2:8 ethylacetate / hexane) to afford (S)-3-tert-Butoxycarbonylamino-4-methoxy-butyric acid benzyl ester as a clear oil . [M-BOC] 224.19.

((S)-3-Hydroxy-1-methoxymethyl-propyl)-carbamic acid tert-butyl ester

A solution of (S)-3-tert-Butoxycarbonylamino-4-methoxy-butyric acid benzyl ester (10.4 g, 32.3 mmol) in dry diethylether (70 ml) cooled to 0°C is treated slowly with a 2.0 M solution of LiBH<sub>4</sub> in THF (32.2 ml, 64.4 mmol). The reaction mixture is allowed to warm to ambient temperature and then left to stir. After 6 hours the reaction mixture is quenched slowly with 0.5 M aqueous solution of citric acid and extracted with ether. The ether phase is dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution with a gradient 3:7 to 6:4 ethylacetate/hexane) to afford ((S)-3-Hydroxy-1-methoxymethyl-propyl)-carbamic acid tert-butyl ester as a clear oil. [M-BOC] 120.13

((S)-3-Iodo-1-methoxymethyl-propyl)-carbamic acid tert-butyl ester

A suspension of polystyrene resin-bound triphenylphosphine (18.645 g, 3 mmol/g) in dry dichloromethane (250 ml) is treated with iodine (12.5 g, 49.22 mmol) and stirred for 15 minutes under argon. Imidazole (3.87 g, 55.94 mmol) is added and the reaction mixture stirred at room temperature for a further 15 minutes. The reaction mixture is then treated with a solution of ((S)-3-Hydroxy-1-methoxymethyl-propyl)-carbamic acid tert-butyl ester (4.9 g, 22.37 mmol) in dichloromethane (30 ml), and refluxed for 1.5 hours under argon. The resin is removed by filtration through a Celite™ filter material pad, washing with dichloromethane. The filtrate is washed with 5% aqueous sodium thiosulphate solution and water, dried over MgSO<sub>4</sub> and evaporated to afford ((S)-3-Iodo-1-methoxymethyl-propyl)-carbamic acid tert-butyl ester as a crude oil. [M-BOC] 230.06.

((R)-3-iodo-1-methyl-propyl)-carbamic acid tert-butyl ester:(S)-3-tert-Butoxycarbonylamino-4-iodo-butyric acid benzyl ester

A suspension of polymer bound triphenyl phosphine (18.25 g, 54.76 mmol) in DCM (100 ml) is treated with iodine (12.2 g, 48.1 mmol) and the reaction mixture stirred at ambient temperature for 15 minutes. Imidazole (3.72 g, 54.7 mmol) is added and the reaction mixture stirred for a further 15 minutes. A solution of (S)-3-tert-butoxycarbonylamino-4-hydroxy-butyric acid benzyl ester (6.76 g, 21.9 mmol) in DCM (100 ml) is added. The suspension is stirred at reflux for 1.5 hours, then filtered through Celite™ filter material, washing through with DCM. The combined organic phase is washed with an aqueous solution of 10% sodium thiosulphate, water and brine, then dried over magnesium sulphate and evaporated. The crude product is chromatographed over flash silica using 8% ethylacetate in iso-hexane as eluent to afford (S)-3-tert-butoxycarbonylamino-4-iodo-butyric acid benzyl ester. [M-BOC] 320.12

((R)-3-Hydroxy-1-methyl-propyl)-carbamic acid tert-butyl ester

A solution of (S)-3-tert-butoxycarbonylamino-4-iodo-butyric acid benzyl ester (0.2 g, 0.477 mmol) in dry diethylether (3 ml) cooled to 0°C under argon, is treated with a 2.0 M solution of lithium borohydride in THF (0.95 ml, 1.9 mmol). The reaction mixture is allowed to warm to ambient temperature with stirring for 18 hours. The reaction is quenched by addition of water and partitioned between ethylacetate and 10% citric acid solution. The organic phase is washed with brine, dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography using 1% methanol in DCM as eluent to afford ((R)-3-hydroxy-1-methyl-propyl)-carbamic acid tert-butyl ester.

((R)-3-Iodo-1-methyl-propyl)-carbamic acid tert-butyl ester

A suspension of polymer bound triphenyl phosphine (0.200 g, 0.595 mmol) in DCM (2 ml) is treated with iodine (0.133 g, 0.523 mmol) and the reaction mixture stirred at ambient temperature for 15 minutes. Imidazole (39 mg, 0.57 mmol) is added and the reaction mixture stirred for a further 15 minutes. A solution of ((R)-3-Hydroxy-1-methyl-propyl)-carbamic acid tert-butyl ester (0.045 g, 0.238 mmol) in DCM (2 ml) is added. The suspension is stirred at reflux for 2.5 hours, then filtered through Celite™ filter material, washing through with DCM. The combined organic phase is washed with an aqueous solution of 10% sodium thiosulphate, water and brine, then dried over magnesium sulphate and evaporated to afford ((R)-3-iodo-1-methyl-propyl)-carbamic acid tert-butyl ester. [M+H] 285.05

5-Ethyl-isoxazol-3-ylamine:(2-Ethyl-[1,3]dioxolan-2-yl)-acetonitrile

A solution of 3-oxo-pentanenitrile (1.582 g, 16.49mmol), ethylene glycol (1.026 ml, 84.59 mmol) and a catalytic amount of p-Toluene sulphonic acid (8 mg) in Toluene (10 ml) is refluxed at 150°C for 2 days using Dean-Stark apparatus. The reaction mixture is diluted with ethyl acetate and washed with saturated sodium bicarbonate solution. The organic phase is dried over MgSO<sub>4</sub>, filtered, and the solvent evaporated to yield (2-ethyl-[1,3]dioxolan-2-yl)-acetonitrile. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 4.15(2H,m), 4.05 (2H, m), 2.65 (2H, s), 1.80 (2H, q), 0.95 (3H, t)

2-(2-Ethyl [1,3]dioxolan-2-yl)-N-hydroxy-acetamidine.

A solution of NaOH (1.17 g, 29.3 mmol) in water/methanol (1:1) (1 8ml), cooled to 0°C in an ice bath, is treated with hydroxylamine hydrochloride (1.58 g, 22.78 mmol), with stirring for 5

minutes. (2-Ethyl-[1,3]dioxolan-2-yl)-acetonitrile (1.42 g, 10.125 mmol) is added and the reaction mixture stirred at room temperature for 18 hours, then refluxed for a further 2 hours. The reaction mixture is cooled and partitioned between ethyl acetate and water. The organic phase is dried over  $\text{MgSO}_4$ , filtered, and the solvent evaporated to yield 2-(2-Ethyl [1,3]dioxolan-2-yl)-N-hydroxy-acetamidine.  $[\text{M}+\text{H}]$  175.21

#### 5-Ethyl-isoxazol-3-ylamine

A solution of 2-(2-ethyl [1,3]dioxolan-2-yl)-N-hydroxy-acetamidine (1.49 g 8.564 mmol) in ethanol (49 ml), acidified to pH 1 with concentrated hydrochloric acid solution, is refluxed at  $50^\circ\text{C}$  for 3 days. The solvent is evaporated and the crude product dissolved in water and extracted into ethyl acetate (x2). The organic phase is dried over  $\text{MgSO}_4$  and evaporated to afford 5-ethyl-isoxazol-3-ylamine.  $[\text{M} + \text{H}]$  113.02

#### (5-Ethyl-[1,3,4]thiadiazol-2-yl)-carbamic acid phenyl ester:

A solution of 5-Ethyl-[1,3,4]thiadiazol-2-ylamine (2.5g, 19.4mmol) and pyridine (1.72 ml, 21.3mmol) in dichloromethane (70 ml) is cooled to  $-70^\circ\text{C}$  and treated with a solution of phenylchloroformate (2.45 ml, 19.6 mmol) in dichloromethane (10 ml) dropwise. The reaction mixture is allowed to warm to ambient temperature and stirred for 3 hours during which a precipitate forms. The precipitate is collected by filtration, and dried under vacuum to afford (5-Ethyl-[1,3,4]thiadiazol-2-yl)-carbamic acid phenyl ester as white solid.  $[\text{M}+\text{H}]$  250.15

#### (5-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid phenyl ester:

A solution of 5-Cyclopropyl-2-methyl-2H-pyrazol-3-ylamine (3.0 g, 22 mmol) (65 ml) and sodium bicarbonate (2 g, 24 mmol) in THF is cooled to  $0^\circ\text{C}$ . Phenylchloroformate (3.4 g, 22 mmol) is added dropwise over 15 minutes. The reaction mixture is allowed to warm to ambient temperature and stirred for 5 hours, then filtered and the filtrate partitioned between ethyl acetate and water. The organic phase is washed with water, 5% aqueous citric acid solution and brine, dried over  $\text{MgSO}_4$  and evaporated to afford (5-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid phenyl ester.  $[\text{M}+\text{H}]$  258.17.

#### (5-Ethyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid phenyl ester:

##### 5-Ethyl-2-methyl-2H-pyrazol-3-ylamine

A solution of 3-Oxo-pentanenitrile (0.5 g, 5.15 mmol) and methylhydrazine (0.24 g, 5.15 mmol) in ethanol (5ml) is heated to reflux for 1.5 hours. The solvent is evaporated and the

residue partitioned between ethyl acetate and brine. The organic phase is dried over  $\text{MgSO}_4$  and evaporated to afford 5-Ethyl-2-methyl-2H-pyrazol-3-ylamine.  $[\text{M}+\text{H}]$

(5-Ethyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid phenyl ester

A solution of 5-Ethyl-2-methyl-2H-pyrazol-3-ylamine (10 g, 79.8 mmol) (500 ml) and potassium carbonate in THF (12.14 g, 87.8 mmol) is cooled to  $0^\circ\text{C}$ . Phenylchloroformate (10.15 ml, 80.6 mmol) is added dropwise over 20 minutes. The reaction mixture is stirred for 40 minutes at  $0^\circ\text{C}$  then allowed to warm to ambient temperature and stirred for a further 2.5 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic phase is washed with 5% aqueous citric acid solution and brine. The organic phase is treated with  $\text{MgSO}_4$  and charcoal then filtered and evaporated to afford (5-Cyclopropyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid phenyl ester.  $[\text{M}+\text{H}]$  246.21

5-Cyclobutyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid phenyl ester:

5-Cyclobutyl-2-methyl-2H-pyrazol-3-ylamine

This is synthesized in an analogous manner to 5-ethyl-2-methyl-2H-pyrazol-3-ylamine except using 3-cyclobutyl-3-oxopropionitrile instead of 3-oxo-pentanenitrile.

5-Cyclobutyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid phenyl ester

A solution of 5-Cyclobutyl-2-methyl-2H-pyrazol-3-ylamine (0.156 g, 1.03 mmol) in dimethylformamide (3 ml) cooled to  $0^\circ\text{C}$ , is treated with phenylchloroformate (0.13 ml, 1.03 mmol) dropwise and left to stir at  $0^\circ\text{C}$  for 1 hour. The reaction mixture is partitioned between ethyl acetate and 1.0 M hydrochloric acid solution, and the organic phase washed with water, dried over magnesium sulphate and evaporated to yield (5-Cyclobutyl-2-methyl-2H-pyrazol-3-yl)-carbamic acid phenyl ester.  $[\text{M}+\text{H}]$  272.22

(2-Ethyl-2H-tetrazol-5-yl)-carbamic acid phenyl ester:

A solution of 2-ethyl-2H-tetrazol-5-ylamine (0.1 g, 0.88 mmol) in dry THF (2 ml) is treated with pyridine (0.09 ml, 1.10 mmol) followed by a solution of phenylchloroformate (0.11 ml, 0.911 mmol) in THF (1 ml). The reaction mixture is stirred at ambient temperature for 1.5 hours, then partitioned between ethyl acetate and water. The ethyl acetate phase is dried over magnesium sulphate and evaporated to afford (2-Ethyl-2H-tetrazol-5-yl)-carbamic acid phenyl ester as a white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz)  $\delta$ , 7.90 (1H, brs), 7.30 (2H, m), 7.15, (3H, m), 4.60 (2H, q) 1.60 (3H, t).

(5-Ethyl-isoxazol-3-yl)-carbamic acid phenyl ester and (3-Ethyl-isoxazol-5yl)-carbamic acid phenyl ester are prepared analogously using 5-Ethyl-isoxazol-3-ylamine and 5-Ethyl-isoxazol-5-ylamine respectively in place of 2-ethyl-2H-tetrazol-5-ylamine.

### Preparation of final compounds

#### Example 1

1-[(S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(3,5-dimethoxy-phenyl)-urea:

##### (a) 1-Benzhydryl-3-(4-chloro-benzenesulfinyl)-azetidine

A solution of 1-Benzhydryl-3-(4-chloro-phenylsulfinyl)-azetidine (3.16 g, 8.6 mmol) in chloroform (30 ml) cooled to -15°C is treated slowly with a solution of meta chloro perbenzoic acid (2.17 g, 8.8 mmol) in chloroform over 2 hours. The reaction mixture is washed with water, aqueous saturated sodium bisulphate solution, sodium bicarbonate solution and brine. The organic phase is dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution with iso-hexane : ether, 7:3 to 1:1) to afford 1-Benzhydryl-3-(4-chlorobenzenesulfinyl)-azetidine, [MH]<sup>+</sup> 384.12.

##### (b) 3-(4-Chloro-benzenesulfinyl)-azetidine

A solution of 1-Benzhydryl-3-(4-chloro-phenylsulfinyl)-azetidine (2.6g, 6.8 mmol) in dichloromethane (35 ml) cooled to -4°C, is treated with 1-chloroethoxycarbonyl chloride (1.25 ml, 11.54 mmol) and the reaction mixture allowed to warm to room temperature with stirring for 18 hours. The solvent is evaporated and the residue taken up in methanol (15 ml) and stirred at room temperature for a further 18 hours. The solvent is evaporated and the residue crystallized from methanol/diethylether to afford 3-(4-Chloro-phenylsulfinyl)-azetidine. [MH]<sup>+</sup> 218.06

##### (c) [(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-[3-(4-chloro-benzenesulfinyl)-azetidin-1-yl]-propyl]-carbamic acid tert-butyl ester

A solution of 3-(4-Chloro-phenylsulfinyl)-azetidine (1.17 g, 4.6 mmol), [(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester (2.8 g, 5.1 mmol) and triethylamine (2.6 ml, 18.4 mmol) in dimethylformamide (35 ml) is stirred at ambient temperature for 18 hours. The reaction mixture is partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase is washed with water and brine,



dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution with dichloromethane: methanol, 95:5 ) to afford {(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-[3-(4-chloro-phenylsulfinyl)-azetidin-1-yl]-propyl}-carbamic acid tert-butyl ester. [MH] + 641.29.

(d) {(S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-carbamic acid tert-butyl ester

A solution of {(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-[3-(4-chloro-phenylsulfinyl)-azetidin-1-yl]-propyl}-carbamic acid tert-butyl ester (2.7 g, 4.21 mmol) in THF (30 ml) is treated with a 1.0 M solution of tetrabutylammonium fluoride in THF (4.21 ml, 4.21 mmol) and the reaction mixture stirred at ambient temperature for 18 hours. The solvent is evaporated and the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase is washed with water and brine, dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution with dichloromethane: methanol, 95:5 ) to afford {(S)-3-[3-(4-Chloro-phenylsulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-carbamic acid tert-butyl ester. [MH ]+ 403.18

(e) (S)-2-Amino-4-[3-(4-chloro-benzenesulfinyl)-azetidin-1-yl]-butan-1-ol

A solution of {(S)-3-[3-(4-Chloro-phenylsulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl}-carbamic acid tert-butyl ester (1.06 g, 2.63 mmol) in dichloromethane (30 ml) is treated with trifluoroacetic acid (7 ml) and stirred at ambient temperature for 2 hours. The solvent is evaporated and the residue partitioned between dichloromethane and sodium hydroxide solution. The DCM phase is dried over magnesium sulphate and evaporated to afford (S)-2-Amino-4-[3-(4-chloro-phenylsulfinyl)-azetidin-1-yl]-butan-1-ol. [M +H] 303.8

(f) 1-[(S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(3,5-dimethoxy-phenyl)-urea

A solution of (S)-2-Amino-4-[3-(4-chloro-phenylsulfinyl)-azetidin-1-yl]-butan-1-ol (0.1 g, 0.264 mmol) and dimethoxyphenylisocyanate (0.048 g, 0.264 mmol) in dichloromethane is stirred at ambient temperature for 2 hours. The solvent is evaporated and the crude product is purified by flash silica chromatography (elution with dichloromethane: methanol, 99:1 to 95:5 ) to afford 1-[(S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(3,5-dimethoxy-phenyl)-urea [MH]+ 484.32

### Examples 2 to 6

The compounds of these Examples, namely 1-((S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-ethyl-[1,3,4]thiadiazol-2)-urea, 1-((S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-ethyl-2-methyl-2H-pyrazol-3-yl)-urea, 1-((S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-urea, 1-((S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-ethyl-isoxazol-3-yl)-urea and 1-((S)-3-[3-(4-Chloro-benzenesulfinyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(3-ethyl-isoxazol-5-yl)-urea are prepared in a manner that is analogous to that described in Example 1.

### Examples 7 to 12

The compounds of these Examples are prepared in a manner that is analogous to that described in Examples 1 to 6 but using ((S)-3-Iodo-1-methoxymethyl-propyl)-carbamic acid tert-butyl ester in place of [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester.

### Examples 13 to 18

The compounds of these Examples are prepared in a manner that is analogous to that described in Examples 1 to 6 but using ((R)-3-iodo-1-methyl-propyl)-carbamic acid tert-butyl ester in place of [(S)-1-(tert-butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester.

### Example 19

1-((S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-urea:

#### (a) 1-Benzhydryl-3-(4-chloro-phenylsulfanyl)-azetidine

A solution of 4-chlorothiophenol (3.0 g, 20.7 mmol) in dimethylformamide (30 ml) is treated with 60% sodium hydride dispersion in mineral oil (1.2 g, 30 mmol), stirred for 10 minutes at ambient temperature, then treated with a solution of methanesulfonic acid 1-benzhydryl-azetidin-3-yl ester (5.98 g, 18.8 mmol) in dimethylformamide (40 ml). The reaction mixture is heated at 60°C for 5 hours, then cooled to ambient temperature and partitioned between ethyl acetate and water. The organic phase is dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution with iso-hexane: ether, 8:2 ) to afford 1-Benzhydryl-3-(4-chloro-phenylsulfanyl)-azetidine as a pale yellow solid.

(b) 3-(4-Chloro-phenylsulfanyl)-azetidine

A solution of 1-Benzhydryl-3-(4-chloro-phenylsulfanyl)-azetidine (0.62 g, 1.7 mmol) in dichloromethane (8 ml) cooled to -4°C, is treated with 1-chloroethoxycarbonyl chloride (0.4 ml, 2.68 mmol) and the reaction mixture allowed to warm to room temperature with stirring for 18 hours. The solvent is evaporated and the residue taken up in methanol (15 ml) and stirred at room temperature for a further 18 hours. The solvent is evaporated and the residue crystallized from methanol/diethylether to afford 3-(4-Chloro-phenylsulfanyl)-azetidine as a white solid.

(c) [(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-[3-(4-chloro-phenylsulfanyl)-azetidin-1-yl]-propyl]-carbamic acid tert-butyl ester

A solution of 3-(4-Chloro-phenylsulfanyl)-azetidine (0.26 g, 1.1 mmol), [(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-iodo-propyl]-carbamic acid tert-butyl ester (0.67 g, 1.21 mmol) and triethylamine (0.62 ml, 4.4 mmol) in dimethylformamide (12 ml) is stirred at ambient temperature for 18 hours. The reaction mixture is partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase is washed with water and brine, dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution with dichloromethane: methanol, 95:5 ) to afford [(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-[3-(4-chloro-phenylsulfanyl)-azetidin-1-yl]-propyl]-carbamic acid tert-butyl ester. [MH] + 625.26.

(d) [(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-carbamic acid tert-butyl ester

A solution of [(S)-1-(tert-Butyl-diphenyl-silanyloxymethyl)-3-[3-(4-chloro-phenylsulfanyl)-azetidin-1-yl]-propyl]-carbamic acid tert-butyl ester (0.612 g, 0.978 mmol) in THF (7 ml) is treated with a 1.0 M solution of tetrabutylammonium fluoride in THF (0.98 ml, 0.98 mmol) and the reaction mixture stirred at ambient temperature for 18 hours. The solvent is evaporated and the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase is washed with water and brine, dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution with dichloromethane: methanol, 95:5 ) to afford [(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-carbamic acid tert-butyl ester. [M ]+ 387.15

(e) (S)-2-Amino-4-[3-(4-chloro-phenylsulfanyl)-azetidin-1-yl]-butan-1-ol

A solution of [(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-

carbamic acid tert-butyl ester (0.22 g, 0.568 mmol) in dichloromethane (7 ml) is treated with trifluoroacetic acid (3 ml) and stirred at ambient temperature for 3 hours. The solvent is evaporated and the residue partitioned between dichloromethane and sodium hydroxide solution. The DCM phase is dried over magnesium sulphate and evaporated to afford (S)-2-Amino-4-[3-(4-chloro-phenylsulfanyl)-azetidin-1-yl]-butan-1-ol.

(f) 1-[(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-urea

A solution of (S)-2-Amino-4-[3-(4-chloro-phenylsulfanyl)-azetidin-1-yl]-butan-1-ol (0.12 g, 0.418 mmol) and (5-Ethyl-[1,3,4]thiadiazol-2-yl)-carbamic acid phenyl ester (0.104 g, 0.418 mmol) in DMSO (2 ml) is stirred at ambient temperature for 4 hours. The reaction mixture is partitioned between ethyl acetate and water. The organic phase is dried over magnesium sulphate and evaporated. The crude product is purified by flash silica chromatography (elution with DCM: methanol, 95:5 to 90:10) to afford 1-[(S)-3-[3-(4-Chloro-phenyl-sulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-urea. [MH]<sup>+</sup> 442.07.

Examples 20 to 24

The compounds of these Examples, namely 1-[(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(5-ethyl-2-methyl-2H-pyrazol-3-yl)-urea, 1-[(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-urea, 1-[(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(3,5-dimethoxy-phenyl)-urea and 1-[(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(5-ethyl-isoxazol-3-yl)-urea and 1-[(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(3-ethyl-isoxazol-5-yl)-urea are prepared in a manner that is analogous to that described in Example 19.

Example 25

1-[(S)-3-[3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-urea:

A solution of 1-[(S)-3-[3-(4-Chloro-phenylsulfanyl)-azetidin-1-yl]-1-hydroxymethyl-propyl]-3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-urea (0.055 g, 0.124 mmol) in dichloromethane (9 ml) cooled to 15°C, is slowly treated with a solution of *meta* chloroperbenzoic acid (0.052 mg, 0.3 mmol) in dichloromethane (2 ml) and stirred for 3 hours. The reaction mixture is diluted with dichloromethane and washed with saturated sodium bicarbonate solution and brine. The organic phase is dried over magnesium sulphate and evaporated. The crude product is purified

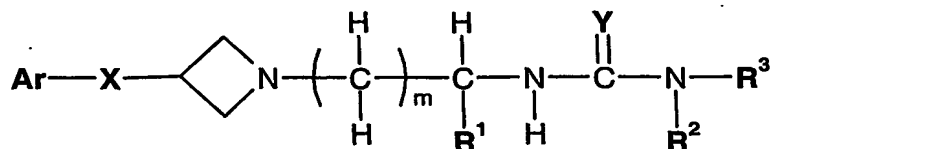
by solid phase extraction using a 2 g Isolute SCX-3 cartridge (elution with methanol, then 5% ammonia in methanol) to afford 1-((S)-3-[3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-ethyl-[1,3,4]thiadiazol-2-yl)-urea. [MH] + 474.11

#### Examples 26 to 30

The compounds of these Examples, namely 1-((S)-3-[3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-ethyl-2-methyl-2H-pyrazol-3-yl)-urea, 1-((S)-3-[3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-cyclopropyl-2-methyl-2H-pyrazol-3-yl)-urea and 1-((S)-3-[3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(3,5-dimethoxy-phenyl)-urea, 1-((S)-3-[3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(5-ethyl-isoxazol-3-yl)-urea and 1-((S)-3-[3-(4-Chloro-benzenesulfonyl)-azetidin-1-yl]-1-hydroxymethyl-propyl)-3-(3-ethyl-isoxazol-5-yl)-urea are prepared in a manner that is analogous to that described in Example 25.

CLAIMS

1. A compound of formula I



in free or salt form, where

Ar is phenyl optionally substituted by one or more substituents selected from halogen, C<sub>1</sub>-C<sub>8</sub>-alkyl, cyano or nitro;

X is -S-, -S(=O)- or -S(=O)<sub>2</sub>-;

m is 1, 2, 3 or 4;

R<sup>1</sup> is hydrogen or C<sub>1</sub>-C<sub>8</sub>-alkyl optionally substituted by hydroxy, C<sub>1</sub>-C<sub>8</sub>-alkoxy, acyloxy, halogen, carboxy, C<sub>1</sub>-C<sub>8</sub>-alkoxycarbonyl, -N(R<sup>4</sup>)R<sup>5</sup>, -CON(R<sup>6</sup>)R<sup>7</sup> or by a monovalent cyclic organic group having 3 to 15 atoms in the ring system;

Y is oxygen or sulfur;

R<sup>2</sup> is hydrogen, C<sub>1</sub>-C<sub>8</sub>-alkyl or C<sub>3</sub>-C<sub>10</sub>-cycloalkyl and R<sup>3</sup> is C<sub>1</sub>-C<sub>8</sub>-alkyl substituted by phenyl, phenoxy, acyloxy or naphthyl, or R<sup>3</sup> is C<sub>3</sub>-C<sub>10</sub>-cycloalkyl optionally having a benzo group fused thereto, a heterocyclic group having 5 to 11 ring atoms of which 1 to 4 are hetero atoms, phenyl or naphthyl, said phenyl, phenoxy or naphthyl groups being optionally substituted by one or more substituents selected from halogen, cyano, hydroxy, acyl, nitro, -SO<sub>2</sub>NH<sub>2</sub>, C<sub>1</sub>-C<sub>8</sub>-alkyl optionally substituted by C<sub>1</sub>-C<sub>8</sub>-alkoxy, C<sub>1</sub>-C<sub>8</sub>-haloalkyl, C<sub>1</sub>-C<sub>8</sub>-alkoxy, C<sub>1</sub>-C<sub>8</sub>-haloalkoxy, C<sub>1</sub>-C<sub>8</sub>-alkylthio, -SO<sub>2</sub>-C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-alkoxycarbonyl, C<sub>1</sub>-C<sub>8</sub>-acylamino optionally substituted on the nitrogen atom by C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-alkylamino, aminocarbonyl, C<sub>1</sub>-C<sub>8</sub>-alkylamino-carbonyl, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)amino, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)aminocarbonyl, di(C<sub>1</sub>-C<sub>8</sub>-alkyl)aminocarbonyl-methoxy, or R<sup>2</sup> and R<sup>3</sup> together with the nitrogen atom to which they are attached denote a heterocyclic group having 5 to 10 ring atoms of which 1, 2 or 3 are hetero atoms;

R<sup>4</sup> and R<sup>5</sup> are each independently hydrogen or C<sub>1</sub>-C<sub>8</sub>-alkyl, or R<sup>4</sup> is hydrogen and R<sup>5</sup> is hydroxy-C<sub>1</sub>-C<sub>8</sub>-alkyl, acyl, -SO<sub>2</sub>R<sup>8</sup> or -CON(R<sup>6</sup>)R<sup>7</sup>, or R<sup>4</sup> and R<sup>5</sup> together with the nitrogen atom to which they are attached denote a 5- or 6-membered heterocyclic group;

R<sup>6</sup> and R<sup>7</sup> are each independently hydrogen or C<sub>1</sub>-C<sub>8</sub>-alkyl, or R<sup>6</sup> and R<sup>7</sup> together with the nitrogen atom to which they are attached denote a 5- or 6-membered heterocyclic group; and

R<sup>8</sup> is C<sub>1</sub>-C<sub>8</sub>-alkyl, C<sub>1</sub>-C<sub>8</sub>-haloalkyl, or phenyl optionally substituted by C<sub>1</sub>-C<sub>8</sub>-alkyl.

2. A compound according to claim 1, in which

Ar is phenyl substituted by halo;

X is -S-, -S(=O)- or -S(=O)<sub>2</sub>-;

m is 2;

R<sup>1</sup> is C<sub>1</sub>-C<sub>8</sub>-alkyl optionally substituted by hydroxy or C<sub>1</sub>-C<sub>8</sub>-alkoxy;

Y is oxygen;

R<sup>2</sup> is hydrogen; and

R<sup>3</sup> is a heterocyclic group having 5 to 11 ring atoms of which 1 to 4 are hetero atoms.

3. A compound according to claim 1, in which

Ar is phenyl substituted by halo;

X is -S-, -S(=O)- or -S(=O)<sub>2</sub>-;

m is 2;

R<sup>1</sup> is C<sub>1</sub>-C<sub>4</sub>-alkyl optionally substituted by hydroxy or C<sub>1</sub>-C<sub>4</sub>-alkoxy;

Y is oxygen;

R<sup>2</sup> is hydrogen; and

R<sup>3</sup> is a heterocyclic group having 5, 6 or 7 ring atoms of which one, two, three or four, are hetero atoms selected from nitrogen, oxygen and sulphur, said heterocyclic group being optionally substituted by C<sub>1</sub>-C<sub>4</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy or C<sub>3</sub>-C<sub>6</sub>-cycloalkyl.

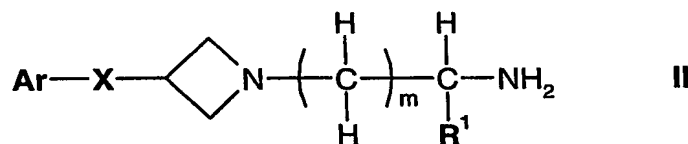
4. A compound according to claim 1 substantially as described in any one of the Examples.

5. A compound according to any one of the preceding claims in combination with another drug substance which is an anti-inflammatory, a bronchodilator or an antihistamine.

6. A compound according to any one of the preceding claims for use as a pharmaceutical.

7. A pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 4.
8. The use of a compound according to any one of claims 1 to 4 for the manufacture of a medicament for the treatment of a condition mediated by CCR-3.
9. Use according to claim 8, in which the condition is an inflammatory or allergic condition, particularly an inflammatory or obstructive airways disease.
10. A process for the preparation of a compound of formula I as claimed in claim 1 which comprises

- (i) (A) for the preparation of compounds of formula I where  $R^2$  is hydrogen, reacting a compound of formula II

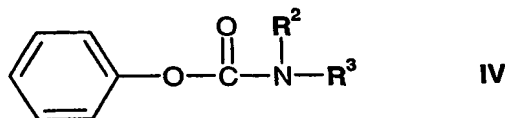


or a protected form thereof, where Ar, X, m and  $R^1$  are as defined in claim 1, with a compound of formula III



where Y and  $R^3$  are as defined in claim 1; or

- (B) for the preparation of compounds of formula I where Y is oxygen, reacting a compound of formula II where Ar, X, m and  $R^1$  are as defined in claim 1, with a compound of formula IV



where  $R^2$  and  $R^3$  are as defined in claim 1; or

- (C) for the preparation of compounds of formula I where X is  $-\text{S}(=\text{O})_2-$ , oxidising a compound of formula I in protected form where X is  $-\text{S}-$  and Ar, m,  $R^1$ , Y,  $R^2$  and  $R^3$  are as defined in claim 1; and

- (ii) recovering the product in free or salt form.



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